| COMBINED TRANSMITTAL OF APPEAL BRIEF TO THE BOARD OF PATENT APPEALS AND INTERFERENCES & PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. 1.136(a) (Large Entity) | Docket No. RLL-170US |
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In Re Application Of:
**RAMPAL et al.**

| Serial No. | Filing Date | Examiner | Group Art Unit |
|---|---|---|---|
| 09/941,970 | August 29, 2001 | Micah Paul Young | 1615 |

Invention: **CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR DERIVATIVE THEREOF**

TO THE COMMISSIONER FOR PATENTS:

This combined Transmittal of Appeal Brief to the Board of Patent Appeals and Interferences and petition for extension of time under 37 CFR 1.136(a) is respectfully submitted by the undersigned:

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*Signature*

Dated: March 25, 2004

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**IN THE BOARD OF APPEALS AND INTERFERENCES**
**OF THE UNITED STATES PATENT & TRADEMARK OFFICE**

Applicant: RAMPAL et al.

Examiner: Micah Paul Young

Application No.: 09/941,970

Group Art Unit: 1615

Filing Date: August 29, 2001

For: **CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR A DERIVATIVE THEREOF**

## BRIEF ON APPEAL

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

1. Real Party in Interest

The real party in interest in this case is Ranbaxy Laboratories Limited, the Assignee of the present application, the assignment being recorded at Reel 012431, Frame 0417.

2. Related Appeals and Interferences

There are no appeals and/or interferences related to this case.

3. Status of Claims

Claims 1, 2, and 5-12 are pending in the application. A copy of the pending claims is provided in the Appendix.

Claims 1, 2, and 5-12 have been finally rejected in the application.

4. Status of Amendments

No amendment has been filed subsequent to the Final Office Action.

5. Summary of Invention

The present invention provides a controlled release formulation of erythromycin A or derivatives thereof that can deliver a daily dose of the drug in a single unit dosage form. The controlled release formulation includes erythromycin A or derivatives that is/are present in the formulation at about 66% w/w to about 90% w/w of the total tablet weight and pharmaceutically acceptable rate controlling polymers that are present in the formulation in very small amounts, namely, from about 0.1 to 4.0% w/w of the total weight of the dosage form.

The present invention also provides a controlled release formulation for once daily administration of erythromycin or derivatives thereof that contains a high dose of the medicament and is of an acceptable size which is convenient for oral administration. The use of small amounts of the rate controlling polymers ensures that total weight of the dosage form is low and a single dosage unit is sufficient to provide the same or similar therapeutic dosage of the drug as compared to administration of two doses of the prior art twice-daily formulation.

6. Issues

Claims 1, 2, and 5-12 are rejected under 35 U.S.C. §103(a).

7. Grouping of Claims

All the claims appealed herein stand or fall together.

8. Argument

a. Claims 1, 2, and 5-12 are unobvious over the prior art combination

Claims 1, 2, and 5-12 have been rejected as being obvious over Talwar et al (WO 00/15198) in view of Fuisz et al (U.S. Patent No. 5,518,730), Ayer et al (U.S. Patent No. 6,096,339) and Misra et al (U.S. Patent No. 5,869,098). Applicants disagree because the art of record does not describe or suggest a controlled release formulation that includes: (1) between about 0.1% w/w to about 4% w/w of rate controlling polymers; and/or (2) between about 66% w/w to about 90% w/w of erythromycin A or a derivative, as recited in the claims.

Talwar discloses a controlled release dosage form that includes an active ingredient, and one or more of a gas generating component, a swelling agent, a viscolyzing agent, gelling polymers, and hydrophilic water-swellable polymers. The dosage form provides a combination of temporal and spatial (e.g., particular portion of the gastrointestinal tract) control over drug delivery. Although Talwar does not specifically define his polymers (i.e., the gas generating component, swelling agent, viscolyzing agent, gelling polymers, and hydrophilic water-swellable polymers) as rate controlling polymers, Talwar's description discloses that these polymers are or function as rate controlling polymers. These rate controlling polymers are present in Talwar's formulations at percentages of between approximately 8% (Table 21) and 50% (Example 6, Table 11) w/w of the tablet.

With respect to the amount of erythromycin A or a derivative, Talwar discloses examples of formulations that include as the active ingredient one of either ciprofloxacin, acyclovir, diltiazem, ranitidine, or captopril. The active ingredient is present in the formulations at percentages of between 37.88% (Example 17) and 88% (Table 22) w/w of the tablet. Thus, as described in greater detail below, Talwar does not describe or

suggest a controlled release formulation that includes: (1) between about 0.1% w/w to about 4% w/w of rate controlling polymers; or (2) between about 66% w/w to about 90% w/w of erythromycin A or a derivative, as recited in the claims. These two points are addressed sequentially below.

b. The art of record does not describe or suggest between about 0.1% w/w to about 4% w/w of rate controlling polymers

Talwar characterizes his formulations as providing a combination of temporal and spatial control of the drug delivery by means of the combination of a gas generating component, a swelling agent, a viscolyzing agent, and, optionally, a gel forming agent, collectively termed a "Controlled Gas Powered System." See Abstract and Page 9, lines 4-10. Talwar notes that the Controlled Gas Powered System is retained for longer periods of time in the stomach than many other dosage forms and, consequently, the drug is released at a constant and controlled rate. See Page 9, line 14 through Page 10, line 2. Talwar also states that hydrophilic water-soluble polymers can be used in the formulations to modify the rate of release of the drug from the composition. See Page 20, line 18 through Page 21, line 4. Although Talwar does not use the term "rate controlling polymer," Talwar's polymers function as rate controlling polymers and many of Talwar's polymers directly correspond to the various rate controlling polymers recited in claims 5-10 of the instant application. These materials that Talwar characterizes as being rate controlling polymers, namely, the gas generating component, swelling agent, viscolyzing agent, gel forming agent, and hydrophilic water-swellable polymers, taken together, make up between 8% and 50% of the tablet by weight.

Again, Talwar does not use the claim term "rate controlling polymer" but nonetheless many of the polymers disclosed in Talwar function as rate controlling polymers. For example, the gas generating component, the swelling agent, and the

viscolyzing agent combine to cause the dosage form to swell to twice its volume. The swelling retains the dosage form in the stomach, thereby extending the time that the dosage form resides in and the drug is delivered to the gastrointestinal tract. See Page 8, line 20 through Page 9, line 13. Talwar gives as examples of swelling agents: cross-linked polyvinylpyrrolidone, cross-linked carboxy methylcellulose sodium, cross-linked carboxy methylcellulose, and sodium starch glycolate. See Page 8, line 20 through Page 9, line 7 and page 17, lines 1-14.

Talwar also discloses that the gel forming polymer or agent produces a cross-linked, stable three-dimensional molecular network or matrix that is retained in the stomach and releases the drug over a sustained period of time. See Page 19, lines 12-18. The gel forming polymer or agent cross-links to form a stable matrix structure such that the matrix structure is retained in the stomach for an extended time. Moreover, Talwar states that "the viscolyzing agent and gel forming polymer provide a tortuous diffusion pathway for the drug, thereby resulting in controlled drug release." See Page 19, lines 18-20. Talwar gives as examples of gel forming polymers alkali metal salts of alginic acid, alkali metal salts of pectic acid, the water soluble salt of polyuronic acid, sodium alginate, potassium alginate, and ammonium alginate. See Page 19, line 20 through Page 20, line 5. Talwar gives as examples of viscolyzing agents carbohydrate gums including xanthan gum, tragacanth gum, gum karaya, guar gum, and acacia. The viscolyzing agent viscolyzes when it contacts the gastrointestinal fluids. See Page 17, lines 15-22 and Page 18, line 15 through page 19, line 2.

Talwar also describes the use of hydrophilic water-soluble polymers in his compositions as useful for modifying the rate of release of the drug from the composition. As examples, Talwar lists hydroxylpropyl methylcellulose, hydroxypropylcellulose, and polyacrylic acid (e.g., Carbopol) as hydrophilic water-soluble polymers. See Page 20, line 18 through page 21, line 7.

Talwar's examples illustrate his use of rate controlling polymers at between 8% (Table 21) and 50% (Example 6, Table 11) w/w of the tablet. For example, the rate controlling polymers of Example 1 are xanthan gum, sodium alginate, cross-linked carboxymethylcellulose, and cross-linked polyacrylic acid (Carbopol), which together make up greater than 14% of the tablet weight. The rate controlling polymers of Example 2 are xanthan gum, sodium alginate, and cross-linked polyvinylpyrrolidone, which together make up greater than 17% of the tablet weight. The rate controlling polymers of Example 3 are xanthan gum, sodium alginate, and cross-linked carboxymethylcellulose, which together make up greater than 9% of the tablet weight. The rate controlling polymers of Example 4 are xanthan gum, sodium alginate, and cross-linked polyvinylpyrrolidone, which together make up greater than 18% of the tablet weight. The remaining examples variously use as rate controlling polymers one or more of xanthan gum, sodium alginate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, and cross-linked polyacrylic acid at total amounts ranging from greater than 8% to greater than 50%.

Neither Fuisz, Ayer, nor Misra, taken separately or in combination with Talwar, cure Talwar's failure to describe or suggest rate controlling polymers making up from 0.1% w/w to about 4% w/w of the total tablet weight. For example, Fuisz discloses using rate controlling polymers at between 50% and 99% w/w of the tablet. See Col. 11, lines 15-52 and Table 1. Ayer discloses using rate controlling polymers at between approximately 17% and 30% w/w/ of the tablet. See Col. 6, lines 17-38, and col. 8, lines, 24-46. Misra discloses using a coating of hydroxypropyl cellulose or hydroxypropyl methyl cellulose, but does not disclose the amount used. See Examples I-VI. Based on these disclosures, one of skill in the art reading Talwar, Fuisz, Ayer, and Misra, separately or in combination, would have found no description or suggestion for reducing

the amount of rate controlling polymer to between 0.1% and 4% w/w/ of the tablet, as recited in claim 1.

As such, Applicants submit that none of the cited references, take separately or in combination, describe or suggest rate controlling polymers making up from 0.1% w/w to about 4% w/w of the total tablet weight and, for at least this reason, independent claim 1 and dependent claims 2 and 5-10 are allowable over Talwar, Fuisz, Ayer, and Misra, taken separately or in combination.

c. The art of record does not describe or suggest between about 66% w/w to about 90% w/w of erythromycin A or a derivative

With respect to the amount of erythromycin, neither Talwar, Fuisz, Ayer, nor Misra describes or suggests a controlled release formulation that contains between about 66% w/w to about 90% w/w of erythromycin A or a derivative. As recognized by the Office Action, Talwar does not disclose any examples with erythromycin or clarithromycin as the pharmaceutically active agent, nor does it specify at what level potential substitutes would be formulated. Instead, Talwar merely lists illustrative drugs "that are suitable for the present invention" and includes clarithromycin in the list. See Col. 7, lines 12-38.

The Office Action states that "substituting and interchanging these compounds is within the level of ordinary skill in the art." Assuming for the sake of argument that it would have been within the level of ordinary skill in the art to interchange clarithromycin and ciprofloxacin, as asserted in the Office Action, the cited references fail to describe or suggest at what dosage strength the clarithromycin would be interchanged. The chemical arts is an unpredictable field and there is no basis upon which one can simply assert that one can interchange compounds, broadly classed as antibiotics, at the same level within a formulation. Each compound has unique physical properties, such as dissolution profile,

spatial bioavailability, and adsorption within the gastrointestinal tract. All of these properties affect the amount or concentration level necessary to impart the intended therapeutic effect of the formulation. As a consequence, Applicants submit that there is no general rule that antibiotics can be substituted in formulations without regard to the formulation or the level of the antibiotic, as apparently asserted by the Office Action.

Specifically, Talwar lacks any description or suggestion of the concentration ranges for which such a substitution of active ingredients would be expected to be successful. Talwar's examples illustrate various active ingredients, of which each contains a varying concentration level of the active ingredient (e.g., from between 37.88% (Example 17) to 88 % (Table 22) w/w of the tablet). Further, Talwar states that the amount of drug "typically ranges from about 0.5 mg up to about 1200 mg", which gives no guidance on the level of clarithromycin to use in place of the various active ingredients disclosed. Even within the group of examples in which Talwar discloses ciprofloxacin, there are varying concentration levels of the active ingredient, namely, approximately 52% (Example 10) to approximately 88% (Table 22).

This lack of teaching or guidance by Talwar would not have sufficiently described or suggested to one skilled in the art that ciproflaxocin and clarithromycin can be interchanged at the same dosage strength and in the same formulation. Applicants submit that only with the present disclosure in hand would one skilled in the art have been motivated to substitute clarithromycin for ciprofloxacin at the same concentration level and in the same formulation as disclosed in Talwar.

Further, neither Fuisz, Ayer, nor Misra, taken separately or in combination with Talwar, cure Talwar's failure to describe or suggest a controlled release formulation that contains between about 66% w/w to about 90% w/w of erythromycin A or a derivative.

Fuisz discloses a controlled release formulation and lists erythromycin as one of more than one hundred other individual bio-active agents. See Col. 7, line 65 through Col. 9, line 8. Assuming for the sake of argument that there would have been some description or suggestion within Fuisz to substitute clarithromycin for ciprofloxacin, there still would have been no description or suggestion to substitute clarithromycin at the same level as the ciprofloxacin disclosed in Talwar. The only disclosure in Fuisz that references an erythromycin derivative is Example 1, in which 200 mg of vancomycin is melt spun into a polymer product and makes up 11% of the product. See Col. 12, lines 51-67 and Table 1. Thus, at most, Fuisz would have motivated one of skill in the art to make a formulation that includes 11% clarithromycin rather than the claimed 66% to about 90% w/w.

Ayers discloses a controlled release formulation in which 500 mg of ciprofloxacin is described as a potential bio-effective agent for incorporation in a tablet. See Example 4. Ayers also states that a large number of active ingredients, including erythromycin, can be used in the dosage form. See Col. 11, line 48 through Col. 12, line 36. Ayers thus discloses that erythromycin can be used in his tablets without disclosing the amount of erythromycin to use. Again, assuming for the sake of argument that there would have been some description or suggestion within Ayer to substitute erythromycin for ciprofloxacin, there would still have been no description or suggestion to substitute erythromycin for ciprofloxacin at the same level as the ciprofloxacin disclosed in Talwar.

Misra discloses a fast dissolving comestible formulation that can include a bio-active agent selected from more than seventy five different classes of drugs as well as from numerous specific drugs, including clarithromycin and ciprofloxacin. See Col. 8, line 53 through Col. 10, line 29; and Col. 12, lines 35-38. However, the amount of clarithromycin or ciprofloxacin to use is not disclosed. The Office Action asserts that it would have been obvious for one of skill in the art to have modified Talwar in view of

Misra to include Misra's clarithromycin. Again, neither Talwar nor Misra has a description or suggestion that clarithromycin can be substituted for ciprofloxacin at the claimed levels.

Accordingly, for at least this additional reason, independent claim 1 and dependent claims 2 and 5-10 are allowable over Talwar, Fuisz, Ayer, and Misra, taken separately or in combination.

d. Independent claims 11 and 12 are allowable for the same reasons that claim 1 is allowable

Independent claim 11 is directed to a monolithic controlled release formulation with 1000 mg of clarithromycin. Like claim 1, there is no description of suggestion in the art of record that clarithromycin could have been substituted for ciprofloxacin without regard to the quantity of ciprofloxacin disclosed. As such, claim 11 is allowable over the art of record for the same reasons that claim 1 is allowable.

Independent Claim 12 is directed to a process for making a controlled release dosage form of erythromycin A or a derivative. Like the dosage form of claim 1, the dosage form of claim 12 includes the erythromycin or derivative being present in an amount from about 66% w/w to about 90% w/w of the total tablet weight and one or more rate controlling polymers making up from about 0.1% to about 4% w/w of the tablet. As such, claim 12 is allowable over the art of record for the same reasons that claim 1 is allowable

## Conclusion

In light of the foregoing, Applicants submit that the claims are not obvious under 35 U.S.C. 103(a). Therefore, the rejection of Claims 1, 2, and 5-12 should be withdrawn and the claims should be allowed.

Respectfully submitted,

Rampal et al.

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APPEAL BRIEF- APPENDIX

PENDING CLAIMS

1. A controlled release formulation of erythromycin A or a derivative thereof, suitable for once daily administration, comprising erythromycin from about 66% w/w to about 90% w/w of the total tablet weight and from about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers.

2. A controlled release formulation as described in claim 1, wherein the erythromycin A derivative is clarithromycin.

5. A controlled release formulation described in claim 1 wherein the pharmaceutically acceptable rate controlling polymer comprises of carbohydrate gum, polyuronic acid salt, cellulose ether, acrylic acid polymer, and mixtures thereof.

6. A controlled release formulation as described in claim 5 wherein the carbohydrate gum is selected from the group consisting of xanthan gum, tragacanth gum, gum karaya, guar gum, acacia, gellan gum, locust bean gum, sclero gum, and mixtures thereof.

7. A controlled release formulation as described in claim 5 wherein the polyuronic acid salt is selected from the group consisting of alkali metal salts of pectic acid, alkali metal salts of alginic acid, and mixtures thereof.

8. A controlled release formulation as described in claim 7 wherein the polyuronic acid salt is preferably sodium alginate.

9. A controlled release formulation as described in claim 5 wherein the cellulose ether are selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropylcellulose, and mixtures thereof.

10. A controlled release formulation as described in claim 5 wherein the acrylic acid polymer is carbopol.

11. A monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin, wherein the total weight of the dosage unit is not more than 1500 mg.

12. A process for the preparation of a controlled release formulation of erythromycin A or a derivative thereof suitable for once daily administration comprising mixing erythromycin or a derivative thereof in an amount from about 66% w/w to about 90% w/w of the total tablet weight with about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers.